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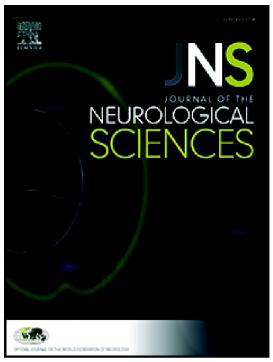

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Peripheral neuropathy in Idiopathic Parkinson's disease: A systematic review.

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Author contributions

PZ and KRC have conceptualized the review. PZ carried out the systematic literature review and wrote the manuscript. RAG, KRC, and MH revised the manuscript.

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Abstract

BACKGROUND: Parkinson's disease (PD) has been associated with peripheral neuropathy (PN). PN has been demonstrated in some rare genetic forms of PD (e.g. PARK2 mutations) but has also been linked to levodopa exposure.

OBJECTIVE: The aim of this systematic review is to clarify any evidence of peripheral nervous system involvement in idiopathic PD.

METHODS: A systematic computer-based literature search was conducted on PubMed database.

FINDINGS: The pooled estimate of the prevalence of large fiber PN in PD was 16.3% (based on 1,376 patients). The pooled estimate of the prevalence of biopsy-proven small fiber neuropathy was 56.9% (based on 72 patients).

Large fiber PN in PD is in the majority of cases distal, symmetrical, axonal and predominantly sensory. There are, however, few reports of chronic idiopathic demyelinating polyneuropathy and very occasional cases of acute neuropathies. Although nerve conduction studies have been performed in the majority of the studies, they included only a limited number of nerves, mainly in the lower limbs.

There is little evidence to support a direct link between levodopa treatment and the development of PN in idiopathic PD. In the majority of the cases PN has been linked to abnormalities in vitamin B12, methylmalonic acid or fasting homocysteine levels. Additional aetiological risk factors for PN may be responsible for any apparent link between PD and PN.

CONCLUSIONS: Large-scale prospective studies with long-term follow-up with detailed baseline assessments are needed in order to understand the natural history of PN in PD, both on clinical and neurophysiological parameters.

1. Introduction

The term peripheral neuropathy (PN) refers to any disorder of the peripheral nervous system including single and multiple mononeuropathies (i.e. mononeuritis multiplex), symmetrical involvement of many nerves (polyneuropathy) or isolated involvement of sensory ganglia (ganglionopathies) [1]. Further classification depends on a mixture of phenomenological, neurophysiological, pathological and aetiological parameters [2]. There is sparse robust epidemiological data on polyneuropathies of any cause in the general population, the current estimates being between 2.4% and 8.0% [3 – 5]. Population-based studies have shown that prevalence of PN increases with age [5], being a common cause of chronic pain in the elderly [6].

An association between PN and Parkinson's disease (PD) has been described in some rare genetic forms of PD, such as in patients with PARK2 mutations [7] and has also been linked to levodopa exposure [8].

The aim of this work was systematically to review available studies on PN in idiopathic Parkinson's disease (IPD) in an attempt to clarify causal mechanisms of peripheral nervous system involvement in IPD.

2. Methods

Literature Search Strategy

A systematic computer-based literature search was conducted on April 9th, 2017 using the PubMed database. For the search we used two Medical Subject Headings (MeSH) terms in title or abstract. Term A was "Parkinson" or "Parkinson's" and Term B was "neuropathy" OR "polyneuropathy". Limitations included human species, English language and full text available. We also perused the reference lists of the papers in order to find papers not identified through the search strategy.

Inclusion and exclusion criteria

To be included in the review, the articles had to meet the following criteria:
(1) to involve single cases or cases series with the combination of PN and IPD,
(2) to study human adult subjects

Exclusion criteria included:

(1) book chapters, reviews, letters to the editor and editorials not providing new data.
(2) Papers referring only to autonomic neuropathy.

3. Results

Search results

This search strategy resulted in the identification of 278 articles. After the eligibility assessment, 243 articles were excluded and 35 met the inclusion criteria. Scanning the reference lists 3 more papers were identified. In total, 38 papers were used for this review. Table 1 summarizes the characteristics of these papers (full details for each study are available as an online Supplement). Figure 1 illustrates the study selection process.

Epidemiology of large fiber neuropathy

Large fiber neuropathy occurs when the Aα and Aβ myelinated fibers are affected and is diagnosed via nerve conduction studies. The first report of patients with PD who developed PN was in 1991 (Bulling et al., [9]). The prevalence of large fiber neuropathy in IPD ranges from 6% to 58% [10 – 12]. The pooled estimate of the prevalence of large fiber neuropathy reported in 17 studies with a total of 1,376 patients was 16.3%. This is higher than the prevalence of PN in the general population [3, 4].

As shown in Table 1, the male:female ratio of patients with PD who developed PN is identical to the gender ratio of the patients with PD who did not develop PN. The mean age of patients who developed PN is higher compared to the mean of the studied populations (69.4 versus 66.0 years respectively).

Epidemiology of small fiber neuropathy

In small fiber neuropathy (SFN), the unmyelinated C and the thinly myelinated Ad fibers are affected. The clinical features (i.e. pinprick and thermal sensory loss, allodynia, hyperalgesia etc.), results of associated special investigations (i.e. quantitative sensory testing and altered intra-epidermal nerve fibre density) and normal nerve conduction studies are used to diagnose SFN [13]. Skin biopsy, as it is objective, appears to have greater diagnostic precision than the clinical examination and quantitative sensory testing in the diagnosis of small fiber neuropathy [14]. Kass-Iliyya et al. recently showed that corneal confocal microscopy could be used as an alternative method to demonstrate non-invasively small nerve fiber damage in PD [15]. In this study it was shown that patients with PD have an increased corneal nerve fiber length and corneal nerve branching density, as well as a decreased corneal nerve fiber density. However, these results were exactly opposite to the ones reported in a study conducted by Podgorny et al. who showed that patients with early PD (drug naïve or recently started on treatment) had significantly reduced corneal nerve fiber densities and lengths compared to controls [16]. Although both studies included small number of patients, and therefore might be underpowered, the contradictory results could also possibly be explained by the fact that the study by Podgorny et al. mainly involved drug-naïve or early treated patients [16].

SFN in PD has been reported since 2008 when Novak et al. demonstrated reduced small fiber density in skin biopsies from patients with PD [17]. Nolano et al. performed quantitative sensory testing and skin biopsies in patients with PD and found a significant increase in tactile and thermal thresholds, a significant reduction in mechanical pain perception and a significant loss of epidermal nerve fibers (ENFs)

and Meissner corpuscles (MCs) in patients with PD compared to controls [18, 19]. Reported prevalence of SFN, as this was determined by the intra-epidermal nerve fiber density, ranges from 37% [20] to 91% [21]. The pooled estimate of the prevalence of small fiber neuropathy based on the skin biopsy as this has been reported in 3 studies of a total of 72 patients with PD is 56.9% [20 – 22]. Given the small number of participants in each study this figure should be interpreted with caution.

Neurophysiological types of chronic neuropathy in PD

Large fiber neuropathies can be broadly classified as axonal, where axons are affected most commonly in proportion to their length (length-dependent polyneuropathy) or demyelinating, affecting the myelin sheath around axons and impairing the ability of the axons to speedily conduct electrical impulses resulting in slow conduction or conduction block [1].

Neuropathy in PD is in the majority of cases distal, symmetrical, axonal and predominantly sensory. There are, however, few reports of chronic inflammatory demyelinating polyneuropathy (CIDP). In their study, Toth et al. reported that out of 49 patients with PD and PN, 94% had sensorimotor axonal neuropathy and 6% had CIDP [23]. In a case series reported by Gondim Fde et al., 1 out of 10 patients reported had CIDP [24]. A case of distal acquired demyelinating symmetric (DADS) neuropathy – which is considered a subtype of CIDP – has been recently reported by McGinty et al. [25] and has been linked with the anti-TNF-α therapy that the patient was receiving for his rheumatoid arthritis. Such reports of patients with PD with co-incident autoimmune diseases [26] suggest a possible role of the immune system in the pathogenesis of at least some cases of neuropathy in PD

Acute polyneuropathies

Isolated cases of patients with PD who developed acute polyneuropathies have been reported. The first such report was by Rajabally et al. [27] who described a patient

who developed acute motor axonal neuropathy (AMAN) following Campylobacter jejuni infection. Acute inflammatory demyelinating polyneuropathy (classical Guillain-Barre syndrome) with positive anti-ganglioside antibodies has been reported by Galazky et al. during intrajejunal levodopa infusion therapy [28].

Pathological findings - nerve biopsies

Sural nerve biopsies have been reported in 2 patients with PD who had developed sub-acute axonal neuropathy associated with cobalamin and vitamin B6 deficiency during intestinal levodopa therapy. The biopsies showed reduction in myelinated nerve fiber density and endoneurial oedema. Myelin debris was found in several endoneurial macrophages, indicating recent nerve fiber breakdown. Inflammatory infiltrates of CD8-immunoreactive T-cells were absent [29]. Evidence of inflammatory changes (perivascular lymphocytic cuffing) had been found in sural nerve biopsies in one of 3 patients reported by Kimber et al. [30] when mild inflammatory infiltration lymphocytes in one out of 2 patients repored by Cáceres-Redondo et al. [31]

Vital et al. conducted a pathological study of peripheral nerves from patients with PN and demonstrated intra-axonal ubiquitin aggregates were more numerous in the patients with PN and PD compared to patients without PD [32]. It is possible that the prevalence of ubiquitin aggregates in patients with PD is the consequence of the underlying neurodegenerative process [32].

Pathological findings – skin biopsies

Small fiber density is reduced in PD compared with healthy controls [15, 18 - 21] and patients with parkinsonism [17, 21] suggesting than skin biopsy may be also contribute to the differential diagnosis of IPD and parkinsonism [21].

Wang et al. studied the α-synuclein deposition in cutaneous sensory nerves and showed that is increased in cutaneous sympathetic adrenergic and sympathetic cholinergic fibers but not sensory fibers of patients with PD compared to controls [21]. Donadio et al. showed that neuritic α-synuclein inclusions are correlated with a small-fiber neuropathy suggesting a possible direct role of phosphorylated α-synuclein in peripheral nerve fiber damage [33].

Risk factors and role of levodopa

The term idiopathic neuropathy refers to those neuropathies where no aetiology can be identified despite extensive and appropriate investigations [1]. The reported prevalence of idiopathic neuropathies among patients with PD varies widely, and investigations about possible causes of polyneuropathy may have been incomplete in some reports [1]. Some studies included in this review have not stated whether extensive thorough investigations were done to identify potential risk factors [34, 35] or, in other studies, the authors have only checked for very common risk factors such as alcohol exposure, diabetes and hypovitaminosis [10, 32, 36, 37].

Toth et al. reported the largest case series of patients with PD and PN [23]. Out of 49 patients with PD and PN, 8 patients were found to have diabetes or impaired glucose tolerance, 4 patients monoclonal gammopathy of uncertain significance and 3 patients had CIDP. Idiopathic PN was identified in 34 patients with PD. However, 32 of these (94%) had abnormalities in vitamin B12, fasting methylmalonic acid (MMA) or fasting homocysteine concentrations (Hcy), leaving only 2 patients (4.1% of the case series) with truly idiopathic neuropathy. In this study, it was suggested that cumulative lifetime levodopa dosage and fasting MMA levels were associated with PN severity and concluded that PN in PD may either be associated with iatrogenic cobalamin metabolic abnormalities or be a peripheral nervous system manifestation of PD [23]. Increased Hcy and low B12 levels have been reported in smaller case series of patients with PD and PN [29 -31, 38 – 43].

Ceravolo et al. reported that the risk of neuropathy in PD is independently associated only to age and duration of exposure to levodopa and is not influenced by disease duration, disease severity, serum vitamin B12 or serum Hcy level [8].

Data on levodopa-naïve patients show that there is no difference between the epidermal nerve fiber density in treated and untreated patients, suggesting that epidermal nerve fiber density is unrelated to drug treatment [19]. In a study conducted by Shahrizaila et al. the electrodiagnostic criteria for distal symmetric polyneuropathy were fulfilled in 24% of treated patients and in 23% of untreated patients, demonstrating no difference in the prevalence of PN in patients with PD taking chronic levodopa therapy versus levodopa-naïve patients [10]. Rajabally et al. found that the prevalence of PN in levodopa-naïve patients with PD was significantly lower compared to levodopa treated (12.1% versus 36.1%) after a regression analysis they concluded that neuropathy was only independently associated with age and serum folate concentration [42].

Protective role of COMT

In a recent study Cossu et al compared 144 patients with PD who have been on levodopa for more than three years not receiving entacapone with 53 patients who have also been on levodopa for more than three years, but were also receiving entacapone [44]. The prevalence of neuropathy in the latter group (prevalence 5.7%) was significantly lower than the patients not receiving entacapone (prevalence 19.4%). This finding, suggests that the use of catechol-O-methyltransferase-inhibitors could have a protective effect on the development of PN.

Intestinal levodopa infusion studies

The first reports of PN during continuous intestinal infusion of levodopa suggested that patients might develop subacute PN secondary to hypovitaminosis, mainly B12

deficiency [29, 38, 39, 45], although isolated case reports described patients with subacute PN without cobalamin deficiency [46].

In a small case controlled study of intestinal levodopa infusion versus oral drugs, Jugel et al. reported that neurophysiological abnormalities were more severe in the group who had intestinal levodopa infusion [35]. Contrary to this finding, Mancini et al. in a large case controlled study compared the prevalence of PN in patients on intestinal levodopa infusion with patients on oral levodopa and with patients on other dopaminergic treatment, and found a higher prevalence of PN in patients treated with intestinal levodopa (28%) and oral levodopa treated patients (20%) compared to patients on other dopaminergic treatments (6%). No difference between the intestinal and oral levodopa groups was observed [37].

In a prospective study of assessment of PN during intestinal levodopa infusion, Merola et al. reported that intestinal levodopa infusion may worsen the neurophysiological and clinical features of pre-existing polyneuropathy, but these alterations are similar to those described during oral levodopa treatment [41]. The same group recently published their experience on 33 consecutive patients treated with intestinal levodopa infusion [47]. Of these, 10 patients (30.3%) had clinical or electrophysiological evidence of PN before the treatment with the intestinal levodopa infusion. Of the remaining 23 patients, almost half (47.8%) developed neuropathy during the intestinal levodopa infusion treatment; 2 developed subacute PN and 9 developed chronic PN (2 with clinical signs and 7 only with electrophysiological evidence).

Chang et al. suggested that clinicians should monitor for PN and for hypovitaminoses during intestinal levodopa infusion, as vitamin supplementation can reverse PN [40]. In a pilot prospective study assessing small nerve fiber impairment following intestinal levodopa infusion in 5 patients, Devigili et al showed that intestinal levodopa infusion could cause severe skin denervation and increased thermal thresholds [48]. Epidermal denervation occured soon after starting treatment; axonal swellings and intraepidermal nerve fiber density reduction were detected

after 3 months, while almost complete denervation of the epidermis and dermal bundles appeared at 6 months [48].

Conclusion

The pooled estimate of the prevalence of large fiber neuropathy in idiopathic PD is estimated to be 16.3%. This is significantly higher compared to the prevalence of PN in the general population. However, this figure should be interpreted with caution, given the heterogeneity of the study populations and the fact that in some studies patients with risk factors such as diabetes and excessive alcohol consumption were excluded. Therefore, the prevalence of PN in PD might be even greater. In addition, the extent of investigations looking at other causes of PN in these patients was variable and often limited.

The role of levodopa on the development of PN is unclear. One study, showed that levodopa is independently associated to PN [42], however the number of patients in that study was too small securely to conclude that levodopa directly is responsible for the development of PN in PD. Available data on levodopa-naïve patients – which are especially important when describing populations of patients with PD [49 – 51] – have not shown difference in the prevalence of PN compared to levodopa treated patients. On the other hand the majority of studies showed that in most PD cases PN is associated with abnormalities in vitamin B12, MMA or and Hcy levels. Such abnormalities can occur as a result of malabsorption and it has been hypothetised that levodopa treatment might affect the vitamin absorption [52].

Although the number of studies of PN in PD is increasing, the number of patients with PD and PN reported in each is small. The largest study to date has included 49 patients with the combination of PD and PN [23]. Large-scale prospective studies with long-term follow-up with detailed baseline assessments are needed in order to understand the natural history of PN in PD, both on clinical and neurophysiological parameters.

Diagnosing PN based on symptom prevalence assessed by checklists and questionnaire has a risk of overestimating the prevalence of PN. This is exaggerated by the fact that patients with PD may experience sensory symptoms, i.e. neuropathic pain of central origin [53] rather than symptoms secondary to PN. PN can only be confirmed by neurophysiological assessment. In most studies included in this review nerve conduction studies (NCS) have been performed and data have been provided, however the NCS included only a limited number of nerves, mainly in the lower limbs. The differences in the techniques, the incomplete NCS and the lack of normative age-corrected data may influence the apparent prevalence of PN in PD. Although many centers have different ways to determine neurophysiologically the presence of neuropathy, sensory conduction studies of sural and radial nerves are recommended for the diagnosis of a mild axonal predominantly sensory neuropathy [54]. This should be complemented with at least one motor study, commonly of the tibial nerve [55], to confirm motor involvement. Early SFN assessment, involving quantitative sensory testing and corneal confocal microscopy may be a useful approach to the diagnosis of PN as it is known that at least some patients evolve from a strict SFN to large fiber PN [56, 57].

Disclosures: Nothing to disclose

Conflict of interest: None

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Figure 1

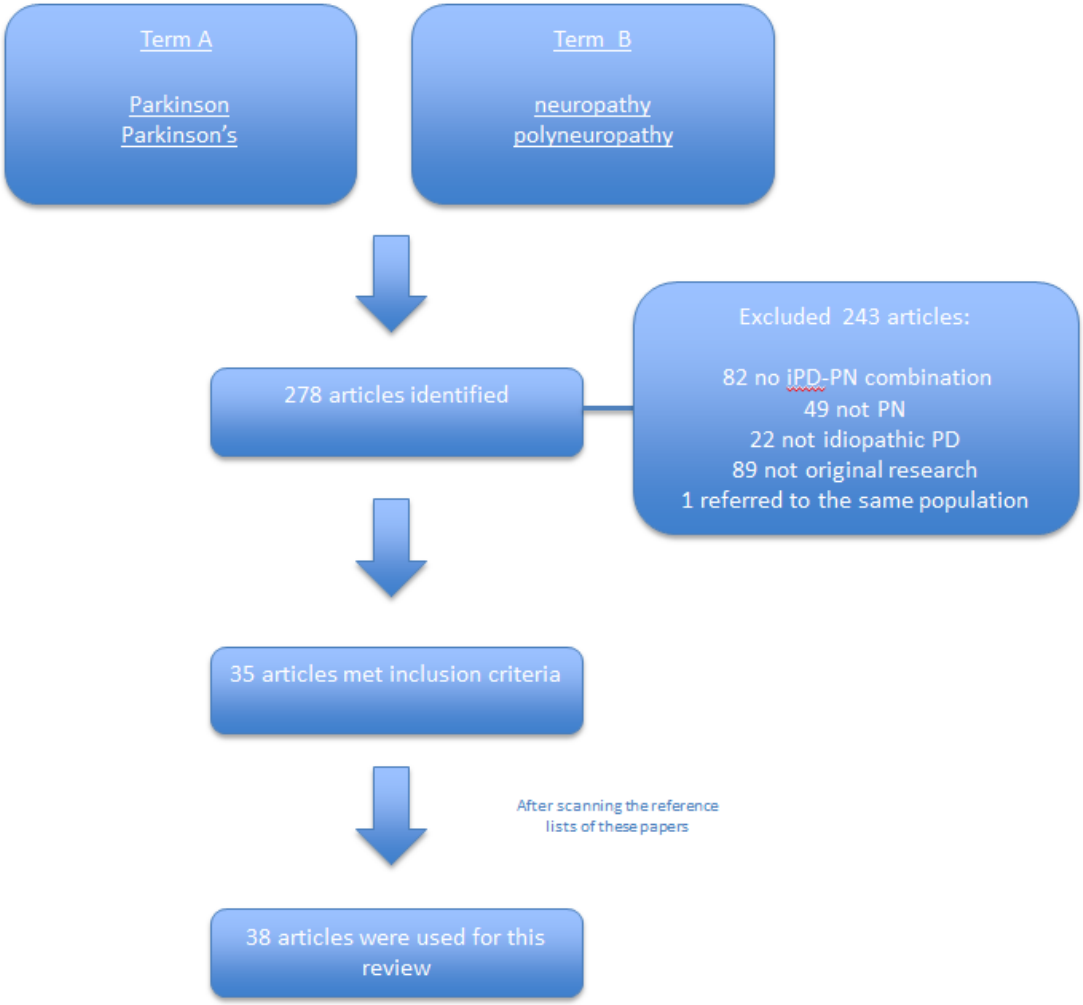

Table 1. Characteristics of papers included in the review. Full details for each study are available as an online Supplement

Types of publications	
Case Reports	4
Case Series / Open label studies	18
Case – controlled studies	16
Number of all PD patients studied	
Total number of PD patients	1,651
Range	1 – 500
Mean number of patients per study (SD)	43.4 (94.5)
Median	20
Demographics of all PD patients studied*	
Male : Female	3:2
Mean age	66.1 years
Mean disease duration	7.9 years
Number of all PD patients with PN studied**	
Total number of PD patients	258
Range	1 – 49
Mean number of patients per study (SD)	7.6 (11.8)
Median	3
Demographics of all PD patients with PN studied*	
Male : Female	3:2
Mean age	69.4 years
Mean disease duration	8.6 years
Year of publication	
Range	1991 to 2016
Number of publications per decade	
Until 2000	1
2000 - 2009	6
2011 – now	31

*where data were provided

**large fiber PN confirmed electrophysiologically

Highlights

- The prevalence of large fiber neuropathy in idiopathic PD is estimated to be 16%
- The role of levodopa on the development of PN is still unclear
- Large studies with neurophysiologically confirmed neuropathy in PD are needed